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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,132	SHUBER, ANTHONY P.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/28/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *10,13,23 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,14-22 and 24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The response filed on 2/28/06 to the restriction requirement of 9/23/05 has been received. Applicant has elected, without traverse, the following species: ras, stool, DNA integrity assay, colonoscopy, colorectal cancer.

The following species of loci have been rejoined: p53 and BAT-26.

Claims 1-32 are pending.

Claims 10, 13, 23, and 32 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-9, 11, 12, 14-22, and 24-31 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11, 12, 14-22, and 24-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 14, 24, and dependant claims 2-9, 11, 12, 15-22, and 25-31 are rejected because claims 1, 14, and 24 are indefinite for reciting: "a predetermined threshold amount". The specification indicates that if the amount of nucleic acid in a sample is greater than "a predetermined threshold amount", then a patient is identified

as a candidate for additional disease testing (paragraph 5, in particular). Further, the specification states: "The predetermined threshold amount is preferably set so that patient samples having an amount of nucleic acids lower than the predetermined threshold amount can be identified as being relatively disease free" (paragraph 5). The specification and the claims do not distinctly claim what is meant by a predetermined threshold amount. It is unclear exactly to what the "predetermined threshold" refers. It is unclear how the exact numeric value of the "predetermined threshold" will be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11, 14-22, and 24-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a patient for the presence of colon cancer and a method of screening for abnormally proliferating colon cancer cells comprising methods using a stool sample, does not reasonably provide enablement for a method of screening a patient for the presence of *any type of disease* using *any type of sample comprising shed cells or shed debris*, screening a patient for *any type of abnormally proliferating cells* using *any type of sample comprising shed cells or shed debris*, and a method of diagnosing *the general state of health of a patient* using *any type of sample comprising shed cells or shed debris*. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are drawn to a method of screening a patient for the presence of *any type of disease* using *any type of sample comprising shed cells or shed debris*, screening a patient for *any type of abnormally proliferating cells* using *any type of sample comprising shed cells or shed debris*, and a method of diagnosing the *general state of health of a patient* using *any type of sample comprising shed cells or shed debris*.

The specification teaches a method of screening a patient for the presence of colon cancer and a method of screening for abnormally proliferating colon cancer cells comprising methods using a stool sample (pages 8-23, in particular).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method of screening a patient for the presence of *any type of disease* using *any type of sample comprising shed cells or shed debris*, screening a patient for *any type of abnormally proliferating cells* using *any type*

of sample comprising shed cells or shed debris, and a method of diagnosing the *general state of health of a patient* using *any type of sample comprising shed cells or shed debris.*

The level of unpredictability for the detection of any disease is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and every type of ailment and every type of sample, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

Further, if an assay is to be used to identify a diseased state, some disease state must be identified in some way with the assay. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test

the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In the instant specification, methods comprising a measure of nucleic acids in stool samples, a measure of mutations in stool samples, and colonoscopies have been shown to predictably diagnose colon cancer (pages 8-23). However, the claimed methods would not predictably detect any and every kind of ailment. Further, stool samples would be the only type of samples that could used in the claimed methods with any predictability of success.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6, 7, 9, 11, 12, 14, 15, 17, 19, 20, 22, 24, 25, 28, 29, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Shuber et al (US 6,268,136 B1).

The claims are drawn to methods for screening a patient for the presence of a disease, screening a patient for abnormal proliferating cells, and a method of diagnosing the state of health of a patient. These methods comprise the steps of measuring a quantitative amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount. The claims are further drawn to methods of performing an assay to detect ras mutations if a patient is identified as a candidate for additional disease testing or if a positive screen is determined. The claims are further drawn to methods wherein the screened disease is cancer or pre-cancer. The claims are further drawn to methods wherein the cancer is colorectal cancer.

Shuber et al teaches methods for screening a patient for the presence of colorectal cancer or pre-cancerous colorectal lesions, screening a patient for abnormal proliferating cells associated with colorectal cancer or pre-cancerous colorectal lesions, and a method of diagnosing the state of health of a patient relating to colorectal cancer or pre-cancerous colorectal lesions (see abstract and columns 2 and 3, in particular). The methods taught by Shuber et al comprise the steps of measuring a quantitative

amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount (see column 2 lines 56-65, in particular). Shuber et al further teaches methods of performing an assay to detect ras mutations if a patient is identified as a candidate for additional disease testing or if a positive screen is determined (see column 5 lines 33-48 and column 6 lines 53-56, in particular).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 12, 14-22, and 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber et al (US 6,268,136 B1) in view of Ahlquist et al

(Gastroenterology, 2000, 119:1219-1227) and Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

Shuber et al teaches as described above.

Shuber et al does not specifically teach methods of determining the number of "genome equivalents" of the measured amount of DNA (claim 3, 16, 26), a method of performing a DNA integrity assay (claims 5, 18, and 27), methods of detecting p53 or BAT-26 mutations (claims 6, 19, and 28), or a method of performing a colonoscopy after the initial screening methods (claims 8, 21, and 30). However, these deficiencies are made up in the teachings of Ahlquist et al and Hromadnikova et al.

Ahlquist et al teaches methods for screening a patient for the presence of colon cancer comprising measuring a quantitative amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount (pages 1221-1224, in particular). Ahlquist et al teaches colorectal cancer patients have higher fecal DNA yields than controls (page 1220 left column). Ahlquist et al further teaches methods of performing a DNA integrity assay (pages 1221-1222, in particular) and an assay to detect ras, p53, and BAT-26 mutations (page 12221 right column, in particular). The method of determining DNA integrity taught by Ahlquist et al comprises two technicians that independently visually determined the amount of high-integrity DNA (page 1222 left column, in particular). Ahlquist et al further teaches colonoscopies as an expensive means of detecting colon cancer (page 1219 right column, in particular). Ahlquist et al further teaches that fecal occult blood

testing may detect cancers at an early stage; however, many cancers and most premalignant adenomas do not bleed and are missed (page 1219 right column, in particular). Thus, Ahlquist et al indicate that the sensitive and specific markers they teach would improve the effectiveness and efficiency of stool screening prior to colonoscopy (page 1219 right column, in particular).

Hromadnikova et al teaches a quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents (page 2 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of screening a patient for the presence of a disease, screening a patient for abnormal proliferating cells, and diagnosing the state of health of a patient using methods taught by Shuber et al with methods of detecting additional mutations associated with colorectal cancer, performing DNA integrity assays, and performing colonoscopies using methods taught by Ahlquist et al. Further, one would have been motivated to do so because Shuber et al stresses the importance of analyzing nucleic acids for genes that have mutations in colorectal cancer. One of skill in the art would be further motivated to combine the teachings of Ahlquist et al with the teachings of Shuber et al because combining multiple assays of detection is know to enhance the accuracy of screening and diagnosis. Further, one would have been motivated to perform colonoscopies after the other screening methods because one of skill in the art would want to perform less expensive and less invasive methods before performing more expensive and more invasive methods such as

colonoscopies. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed screening methods since detection of mutations, DNA integrity assays, and colonoscopies are well known and conventional in the art. Further, it would have been obvious to quantitate methods involved in comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because using the quantitative method taught by Hromadnikova et al would be an effective way of normalizing data between multiple assays. Further, determining the number of genome equivalents as taught by Hromadnikova et al would reduce technical errors that would occur with methods of Ahlquist et al. Further, one of skill in the art would have a reasonable expectation of success in determining the number of genome equivalents since determining the number of genome equivalents in a sample is well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations and the method of Shuber et al teaches quantitating the DNA before performing methods of detecting mutation.

Claims 1-9, 11, 12, 14-22, and 24-31 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Ahlquist et al (Gastroenterology, 2000, 119:1219-1227) in view of Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims are drawn to methods for screening a patient for the presence of a disease, screening a patient for abnormal proliferating cells, and a method of diagnosing the state of health of a patient. These methods comprise the steps of measuring a quantitative amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount. The claims are further drawn to a method wherein the measuring comprises determining number of genome equivalents. The claims are further drawn to methods of performing a DNA integrity assay or an assay to detect ras, p53, and BAT-26 mutations if a patient is identified as a candidate for additional disease testing or if a positive screen is determined. The claims are further drawn to methods of performing colonoscopies on patients identified as candidates for additional disease testing and on patients with a positive screen. The claims are further drawn to methods wherein the screened disease is cancer or pre-cancer. The claims are further drawn to methods wherein the cancer is colorectal cancer.

Ahlquist et al teaches methods for screening a patient for the presence of colon cancer comprising measuring a quantitative amount of genomic DNA in a stool sample, and identifying the patient as a candidate for additional disease testing or identifying patients with a positive screen if the amount of nucleic acid is above a predetermined

threshold amount (pages 1221-1224, in particular). Alhlquist et al teaches colorectal cancer patients have higher fecal DNA yields than controls (page 1220 left column). Ahlquist et al further teaches methods of performing a DNA integrity assay (pages 1221-1222, in particular) and an assay to detect ras, p53, and BAT-26 mutations (page 12221 right column, in particular). The method of determining DNA integrity taught by Ahlquist et al comprises two technicians that independently visually determined the amount of high-integrity DNA (page 1222 left column, in particular). Ahlquist et al further teaches colonoscopies as an expensive means of detecting colon cancer (page 1219 right column, in particular). Ahlquist et al further teaches that fecal occult blood testing may detect cancers at an early stage; however, many cancers and most premalignant adenomas do not bleed and are missed (page 1219 right column, in particular). Thus, Ahlquist et al indicate that the sensitive and specific markers they teach would improve the effectiveness and efficiency of stool screening prior to colonoscopy (page 1219 right column, in particular).

Ahlquist et al does not specifically teach a method wherein the measuring comprises quantitatively determining number of genome equivalents. Further, Ahlquist et al does not specifically teach the exact sequence that the pre-colonoscopy screening steps should be performed. However, these deficiencies are rendered-obvious or made up in the teachings of Hromadnikova et al.

Hromadnikova et al teaches a quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents (page 2 right column, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screening a patient for the presence of colon cancer or the abnormally proliferating cells of colon cancer by using methods taught by Ahlquist et al with the quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because using a quantitative method of comparing samples would reduce the technical errors that would occur with the method of Ahlquist et al, which uses highly subjective means of comparing samples. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since comparing amounts of DNA between samples comprising determining the number of genome equivalents is well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9, 11, 12, 14-22, and 24-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-7 of copending Application No. 11/090479 in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227) and Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims of Application 11/090479 are drawn a method of screening a patient for cancer or precancer comprising a DNA integrity assay.

The claims of Application 11/090479 do not teach the other screening steps of the claims. However, these deficiencies are made-up in the teachings of Ahlquist et al and Hromadnikova et al.

Ahlquist et al and Hromadnikova et al teach as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screening a patient for the presence of colon cancer or the abnormally proliferating cells of colon cancer by using methods of claims

6-7 of copending Application No. 11/090479 with the other methods of screening for colon cancer as taught by Ahlquist et al and with the quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because combining screening methods would give rise to a more accurate diagnosis and using a quantitative method of comparing samples would reduce the technical errors. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since the screening methods taught by Ahlquist et al and methods of comparing amounts of DNA between samples comprising determining the number of genome equivalents are well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations.

This is a provisional obviousness-type double patenting rejection.

Claims 1-9, 11, 12, 14-22, and 24-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,919,174 B1 in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227) and Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims of U.S. Patent No. 6,919,174 B1 are drawn a method of screening a patient for cancer or precancer comprising a DNA integrity assay.

The claims of U.S. Patent No. 6,919,174 B1 do not teach the other screening steps of the claims. However, these deficiencies are made-up in the teachings of Ahlquist et al and Hromadnikova et al.

Ahlquist et al and Hromadnikova et al teach as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screening a patient for the presence of colon cancer or the abnormally proliferating cells of colon cancer by using methods of claims the claims of U.S. Patent No. 6,919,174 B1 with the other methods of screening for colon cancer as taught by Ahlquist et al and with the quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because combining screening methods would give rise to a more accurate diagnosis and using a quantitative method of comparing samples would reduce the technical errors. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since the screening methods taught by Ahlquist et al and methods of comparing amounts of DNA between samples comprising determining the number of genome equivalents are well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would

be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations.

Claims 1-9, 11, 12, 14-22, and 24-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,964,846 B1 in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227) and Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims of U.S. Patent No. 6,964,846 B1 are drawn a method of screening a patient for cancer or precancer comprising a DNA integrity assay.

The claims of U.S. Patent No. 6,964,846 B1 do not teach the other screening steps of the claims. However, these deficiencies are made-up in the teachings of Ahlquist et al and Hromadnikova et al.

Ahlquist et al and Hromadnikova et al teach as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screening a patient for the presence of colon cancer or the abnormally proliferating cells of colon cancer by using methods of claims the claims of U.S. Patent No. 6,964,846 B1 with the other methods of screening for colon cancer as taught by Ahlquist et al and with the quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because combining screening methods would give rise to a more accurate

diagnosis and using a quantitative method of comparing samples would reduce the technical errors. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since the screening methods taught by Ahlquist et al and methods of comparing amounts of DNA between samples comprising determining the number of genome equivalents are well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations.

Claims 1-9, 11, 12, 14-22, and 24-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 6,143,529 in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227) and Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims of U.S. Patent No. 6,143,529 are drawn a method of screening a patient for cancer or precancer comprising a DNA integrity assay. The claims are further drawn to detecting mutations in order to diagnose colon cancer.

The claims of U.S. Patent No 6,143,529 do not teach the other screening steps of the claims. However, these deficiencies are made-up in the teachings of Ahlquist et al and Hromadnikova et al.

Ahlquist et al and Hromadnikova et al teach as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to screening a patient for the presence of colon cancer or the abnormally proliferating cells of colon cancer by using methods of claims the claims of U.S. Patent No. 6,143,529 with the other methods of screening for colon cancer as taught by Ahlquist et al and with the quantitative method of comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because combining screening methods would give rise to a more accurate diagnosis and using a quantitative method of comparing samples would reduce the technical errors. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed method since the screening methods taught by Ahlquist et al and methods of comparing amounts of DNA between samples comprising determining the number of genome equivalents are well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations.

Claims 1-9, 11, 12, 14-22, and 24-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 31-48 of U.S. Patent No. 6,268,136 B1 in view of Ahlquist et al (Gastroenterology, 2000, 119:1219-1227) and Hromadnikova et al (BMC Pregnancy and Childbirth, 5/28/02, 2(4):1-5).

The claims of U.S. Patent No. 6,268,136 B1 are drawn to methods for screening a patient for the presence of colorectal cancer or pre-cancerous colorectal lesions, screening a patient for abnormal proliferating cells associated with colorectal cancer or pre-cancerous colorectal lesions, and a method of diagnosing the state of health of a patient relating to colorectal cancer or pre-cancerous colorectal. The claims of U.S. Patent No. 6,268,136 B1 further comprise methods of measuring a quantitative amount of genomic DNA in a stool sample, and identifying a patient as a candidate for additional disease testing or identifying patients with a positive screen if the amount of nucleic acid is above a predetermined threshold amount. The claims are further drawn to methods of performing an assay to detect mutations if a patient is identified as a candidate for additional disease testing or if a positive screen is determined.

The claims of U.S. Patent No. 6,268,136 B1 does not teach the other screening steps of the claims. However, these deficiencies are made-up in the teachings of Ahlquist et al and Hromadnikova et al.

Ahlquist et al and Hromadnikova et al teach as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of screening a patient for the presence of a disease, screening a patient for abnormal proliferating cells, and

diagnosing the state of health of a patient using methods found in the claims of claims of U.S. Patent No. 6,268,136 B1 with methods of detecting specific mutations associated with colorectal cancer, performing DNA integrity assays, and performing colonoscopies using methods taught by Ahlquist et al. Further, one would have been motivated to do so because claims of U.S. Patent No. 6,268,136 B1 stresses the importance of analyzing nucleic acids for genes that have mutations in colorectal cancer. One of skill in the art would be further motivated to combine the teachings of Ahlquist et al with the claims of claims of U.S. Patent No. 6,268,136 B1 because combining multiple assays of detection is know to enhance the accuracy of screening and diagnosis. Further, one would have been motivated to perform colonoscopies after the other screening methods because one of skill in the art would want to perform less expensive and less invasive methods before performing more expensive and more invasive methods such as colonoscopies. Further, one of skill in the art would have a reasonable expectation of success in performing the claimed screening methods since detection of mutations, DNA integrity assays, and colonoscopies are well known and conventional in the art. Further, it would have been obvious to quantitate methods involved in comparing amounts of DNA between samples comprising determining the number of genome equivalents as taught by Hromadnikova et al. Further, one would have been motivated to do so because using the quantitative method taught by Hromadnikova et al would be an effective way of normalizing data between multiple assays. Further, determining the number of genome equivalents as taught by Hromadnikova et al would reduce technical errors that would occur with methods of

Ahlquist et al. Further, one of skill in the art would have a reasonable expectation of success in determining the number of genome equivalents since determining the number of genome equivalents in a sample is well known and conventional in the art. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to compare DNA yields from patients with colorectal cancer than from controls *prior* to performing the DNA integrity assay or detection of mutation assay. Further, one would be motivated to do so because one would routinely determine the amount of total DNA in a sample in preparation for performing DNA integrity assays or assays detecting mutations and the method of Shuber et al teaches quantitating the DNA before performing methods of detecting mutation.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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SEA

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